

## REMARKS

### Status of the Claims

Claims 1-44 were withdrawn from consideration and are now canceled. Claims 45-82 are pending. Claims 45-67 and 70-82 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Claims 51, 52, 59, 60, 63, and 77-82 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 45-48, 54-59, 61-65, 70, 71, and 72 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-57 stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349. Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349, further in view of Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-82 also stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claim 22 of US Patent 6,495,550 and claims 30-59 of US Patent 6,737,422.

### The Invention

Applicants have demonstrated for the first time that openers of KCNQ potassium channels alleviate anxiety. The mechanism for treating anxiety by opening KCNQ potassium channels was previously unknown. Applicants have demonstrated the efficacy of this discovery using an *in vivo* experimental procedure routinely used by the pharmaceutical industry to screen for and identify drugs effective for the treatment of generalized anxiety disorder. The present application therefore provides not only a mechanism for treating anxiety disorders, but also a large number of structurally diverse compounds that open KCNQ potassium channels as well as assays for identifying compounds that open KCNQ potassium channels and reduce anxiety.

**Rejection under 35 U.S.C. §112, first paragraph**

**Introduction**

Claims 45-67 and 70-82 stand rejected as allegedly containing subject matter that was not enabled by the specification as originally filed. The Examiner asserts that while the application is enabling for the aryl amide compounds of Figure 7, it does not provide enablement for other compounds "that are functionally described as being known as a compound the increases ion flow through KCNQ potassium channels in a cell." Office Action, page 5. Applicants respectfully traverse this rejection. First, the Examiner has improperly rejected the claims as both lacking enablement and obvious over the prior art cited for the purposes of obviousness and obviousness-type double patenting. If the prior art is enabling, as it must be to serve as a proper 103 reference, then so too is the present application. Furthermore, the specification sets forth assays to determine the ability of KCNQ channel openers to treat anxiety, as well as working examples of such compounds. Given the disclosed assays, working examples, and level of skill in the art, the skilled artisan can easily, with no more than routine experimentation, identify compounds useful for the claimed methods.

**Rejection of a claim as lacking enablement and as obvious over the prior art is improper**

The Examiner has rejected the present claims as allegedly obvious over US Patent 6,235,758 and as allegedly unpatentable for obviousness type double patenting over US Patent 6,593,349 (further in view of US Patent 6,235,758); US Patent 6,495,550, and US Patent 6,737,422. As prior art references, these references are presumed to be enabled and operable until shown otherwise. MPEP § 2121. Therefore, it is improper for the Examiner to assert that the cited prior art references are enabling, but that the present application is not. Applicants therefore request that the enablement rejection be withdrawn.

**The law regarding fulfillment of the enablement requirement**

The Examiner has rejected the claims as lacking enablement commensurate with the scope of the claims, citing *In re Wands*. The Examiner appears to be concerned that the

claims encompass a broad genus of compounds. However, routine screening of large numbers of samples does not constitute undue experimentation under *Wands*. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

In *Wands*, the Federal Circuit held that the specification was enabling and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known" *Wands* at 1406. The same is true of the present application. Indeed, the patentee in *Wands* made experimental attempts to identify 143 "high-binding" hybridomas from 10 myeloma-B lymphocyte fusions (of which four fusions completely failed), and then identified only four hybridomas of interest from the 143 "high binders." *Wands* at 1405. The applicant in *Wands* carried out the procedure for making a monoclonal antibody three times and each time successfully produced at least one such antibody. Although the Applicant in *Wands* performed what might be considered as a considerable amount of experimentation, this quantity of experimentation is permissible under the enablement requirement, since the experimentation is merely routine and not undue.

Furthermore, as stated by the MPEP § 2164.02, the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure. Because only an enabling disclosure is required, Applicant need not describe all actual embodiments. For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient. The present application has certainly complied with this standard.

To make a valid rejection, the Examiner must state why one would not expect to be able to extrapolate the example across the entire scope of the claims. MPEP § 2164.02. However, the Examiner has not provided convincing evidence why one of skill in the art would not be able to use the same assays used to identify the compounds of Example 1 to identify and

use additional compounds commensurate in scope with the claims. In fact, beyond listing the *Wands* factors, the Examiner has failed to provide any technical reasoning why the present application lacks enablement.

Finally, the presence of inoperative embodiments in the scope of the claim does not render a claim lacking enablement if only routine experimentation is required to determine which embodiments are operative. MPEP § 2164.08(b).

### **Disclosure of Assays to Identify KCNQ Channel Openers**

The point of novelty of the present invention lies in the discovery of a new mechanism of treating anxiety by increasing ion flow through KCNQ potassium channels. This novel mechanism is repeatedly disclosed throughout the specification, for example, at page 3, lines 14-20; page 3, lines 23-25, page 3 line 32 to page 4, line 4; page 12, line 4 to page 6, line 13; and Example 6. Applicants respectfully assert that the disclosure of this novel mechanism, coupled with the extensive teachings and examples set forth in the specification as outlined below, satisfies the legal requirements for enablement for obtaining method claims to anxiety treatments based on the administration of chemical agents that are defined solely by their function as KCNQ channel openers, without structure.

The specification sets forth a number of assays to identify KCNQ channel openers. The assays involve the *in vivo* or *in vitro* treatment of a sample containing a KCNQ channel with a potential KCNQ channel opener and subsequent measurement of the KCNQ potassium channel activity. See specification, page 23, lines 25-29. The activity of the test compound may then be compared with untreated control samples. See specification, page 23, lines 27-29. Such assays can be conducted using high throughput screening methods and large libraries of chemical compounds, which are well known in the art, and systematic screening of potential KCNQ channel openers can be aided by robotic automation. See specification, page 25, lines 21-27. KCNQ potassium channel opening activity may be determined by measuring changes in ion flux through detection of cell or membrane polarization. See specification, page 24, lines 4-6. Cell or membrane polarization is detected by measuring changes in current using standard techniques such as voltage clamps or patch clamps. See specification, page 24, lines 6-

10. These assays can be used routinely to determine whether or not a selected compound acts as a KCNQ channel opener.

Other standard assays for measuring ion flux are also disclosed, such as those involving the measurement of potassium or rubidium ions flux by directly detecting the concentration changes of the ions (e.g., radioisotopic labeling). See specification, page 24, lines 23-32. In addition, ion flux may be measured by determining changes in physiological conditions, such as transmitter release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as  $\text{Ca}^{2+}$ , or cyclic nucleotides. See specification, page 24, line 30 to page 25, line 8.

At page 23, lines 12-18, the specification further provides an array of methods useful in identifying KCNQ channel openers, including:

measuring current; measuring membrane potential;  
measuring ion flux; e.g., potassium or rubidium;  
measuring potassium concentration; measuring  
second messengers and transcription levels, using  
potassium-dependent yeast growth assays;  
measuring pain responses in mice, e.g., with  
formalin algnesia or hotplate assays; measuring  
ligand binding; and using, e.g., voltage-sensitive  
dyes, radioactive tracers, and patch-clamp  
electrophysiology.

Moreover, the assays set forth in the specification were well known in the art at the time of filing the application. The fact that these methods were well known in the art is supported by the references cited in the specification, such as:

Ackerman *et al.*, *New Engl. J. Med.* 336:1575-1595 (1997);  
Hamil *et al.*, *Pflugers. Archiv.* 391:85 (1981);  
Vestergaard-Bogind *et al.*, *J. Membrane Biol.* 88:67-75 (1988);  
Daniel *et al.*, *J. Pharmacol. Meth.* 25:185-193 (1991);

Holevinsky *et al.*, *J. Membrane Biology* 137:59-70 (1994);  
Blatz *et al.*, *Nature* 323:718-720 (1986); and  
Park, *J. Physiol.* 481:555-570 (1994).

The Examiner has presented no evidence or reasoning as to why one skilled in the art would doubt the routine use of the functional assays disclosed in the specification or well known in the art. Therefore, after examining the assays set forth in the specification and reviewing assays well known in the art, one skilled in the art would conclude that Applicants enabled methods for identifying and using potassium channel openers.

#### **Disclosure of Assays to Determine the Ability of Channel Openers to Treat Anxiety**

The specification also sets forth assays to test potassium channel openers for their ability of treat anxiety. Again, these assays can be used routinely to identify operable embodiments of the invention. On page 12, line 16 to page 13, line 3, the specification provides a detailed description of assays useful in testing anxiolytic effects:

The standard test in rat to measure anxiolytic effect (Geller conflict procedure) was designed by Geller and Seifter and modified by Pollard and Howard (Geller & Seifter, *Psychopharmacologia* 1:482-492 (1960); Pollard & Howard, *Psychopharmacology* 62:117-121 (1979)). The anxiety-reducing effect of a KCNQ2/3 channel opener was measured using the Geller conflict procedure in rats. Rats are trained to press a lever to receive food pellets during daily 1 hour sessions. The sessions are divided into punished and unpunished phases. During the four, three-minute punished periods, a light signals that each lever press will produce both a pellet and a foot shock (punishment), which reduces lever pressing. The number of punished lever presses on test days (when test compound is administered) is compared to the mean on baseline days. The positive control, chlordiazepoxide, increases punished lever pressing by > 50%. A compound that produces an increase of approximately 40% or greater is generally considered to be of interest as a rapid-onset anxiolytic. A selective KCNQ2/3 channel opener increased punished responding in a dose dependent, statistically significant manner (Figure 6).

Again, these assays are well known in the art, as evidenced by the multiple citations in the above passage. The Examiner has not questioned the validity of these methods or provided reasoning as to why one skilled in the art would doubt the usefulness of the disclosed assays. Thus, Applicants assert that one skilled in the art, using the teachings in the specification and methods generally known in the art, would be able to determine the ability of KCNQ channel openers to treat anxiety in a subject. Absent some reasoning or evidence to doubt the usefulness of the methods disclosed in the specification, Applicants submit that one skilled in the art would recognize that Applicants fully enabled a methods of identifying a KCNQ potassium channel opener useful in treating anxiety.

**The specification sets forth large number of structurally diverse compounds able to increase ion flow through KCNQ potassium channels**

The specification sets forth a large number of structurally diverse KCNQ channel openers representative of the scope of the claims. For example, the specification discloses a structurally diverse genus of KCNQ channel openers able to increase ion flow through KCNQ potassium channels. See page 4, line 29 to page 9, line 19.

Furthermore, contrary to the Examiner's assertion, Figure 7 sets forth a list of exemplary KCNQ channel openers much more diverse than N-aryl benzylamides. The following exemplary KCNQ channel openers are disclosed in Figure 7:

- N-aryl oxazole amides;
- N-aryl furan amides;
- N-aryl thiazole amides;
- N-aryl thiadiazole amides;
- N-aryl isothioazole amides;
- N-aryl imidazole amides;
- N-aryl pyrazole amides;
- N-aryl triazole amides;
- N-aryl thiophene amides;
- N-aryl indole amides;

N-aryl purine amides;  
N-aryl benzoimidazole amides;  
N-aryl benzofurane amides;  
N-aryl benzothiophene amides;  
N-aryl benzoisothiazole amides; and  
N-aryl benzylamides.

In addition to the KCNQ channel openers set forth in Figure 7, the specification also discloses a diverse array of KCNQ channel openers set forth in USSN 60/158,712, filed October 8, 1999, from which the current application claims priority. USSN 60/158,712 discloses a variety of N-aryl, N-alkyl, and N-cycloalkyl pyrazole amide KCNQ channel openers. Any one of these channel openers can be routinely tested for the ability to treat anxiety, using the assays disclosed in the invention.

#### **A working example of in vivo treatment of anxiety**

The specification provides a working example of the claimed invention in which a KCNQ channel opener is administered in accordance with the protocol of the Geller conflict model. See Example 6. This example demonstrates that the invention as claimed works for its intended purpose. The Examiner has presented no evidence or reasoning as to why one skilled in the art would doubt the validity of this experiment. Moreover, the Examiner has presented no evidence or reasoning as to why one skilled in the art, after examining this experiment, would conclude that a KCNQ channel opener would *not* work as intended in claims 45-57.

Therefore, Applicants respectfully submit that one skilled in the art would recognize that Applicants enabled a method of reducing anxiety using a compound that increases ion flow through a KCNQ potassium channel as claimed.

#### **Summary of Applicants' Disclosure**

In sum, Applicants' disclosure sets forth:

- (a) Methods to identify KCNQ channel openers;
- (b) Methods to test KCNQ channel openers for their ability to treat anxiety;



(c) A large number of structurally diverse compounds capable of increasing ion flow through KCNQ potassium channels; and

(c) A working example of the claimed invention.

Therefore, one skilled in the art would necessarily conclude that Applicants have enabled a method for treating anxiety using *any* KCNQ channel opening compound regardless of the actual structure of the KCNQ channel opener. Furthermore, as stated above, the Examiner has improperly rejected the claims as both lacking enablement and as obvious over patents that are presumed to be enabled, with no more disclosure than that of the Applicants application. If the cited prior art is enabled, then Applicants application must be enabled as well. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §112, first paragraph.

**Rejection under 35 U.S.C. §112, second paragraph**

Claims 51 and 52 were rejected as allegedly indefinite for referring to a "heteromeric KCNQ channel" without adequate antecedent basis. These claims have been amended to refer to claim 49, which refers to a "heteromeric KCNQ channel." Applicants respectfully request that the rejection be withdrawn.

Claims 59, 60, 63, and 77-82 were rejected as referring to R group variables with typographical errors in the subscript formatting. The claims have been amended to correct the typographical errors. Applicants respectfully request that the rejection be withdrawn.

**Rejections under 35 U.S.C. §103(a)**

**Introduction**

Claims 45-48, 54-59, 61-65, 70, 71 and 72 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Gaster *et al.*, U.S. Patent No. 6,235,758 (hereinafter referred to as "Gaster"). The Examiner asserts that Applicants' invention merely elucidates a mechanistic step that is inherent in the administration of the aryl carbamoyl compounds of Gaster. The Examiner

reasons that because this mechanistic step is inherent in the aryl carbamoyl compounds of Gaster, it would have been obvious for one skilled in the art to treat anxiety as claimed.

### **Burden of Proof in Establishing Prima Facie Obviousness**

"The examiner bears the burden of establishing a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Only if this burden is met does the burden of coming forward with rebuttal arguments or evidence shift to the applicant. *Rijckaert*, 9 F.3d at 1532, 28 USPQ2d at 1956. When the references cited by the examiner fail to establish a *prima facie* case of obviousness, the rejection is improper and will be overturned. *In re Fine*, 837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988)." See *In re Deuel*, 51 F.3d 1552, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

In order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

As explained below, Applicants submit that the cited reference does not teach all the claimed elements, namely, the use of KCNQ channel openers to treat anxiety, and fails to provide a basis for the skilled artisan to reasonably expect that the disclosed compounds are useful for treating anxiety by increasing ion flow through KCNQ potassium channels. Also enclosed is an expert declaration of Dr. Alan Wickenden, which explains why one of skill in the art would not view Gaster as teaching or disclosing, either explicitly or inherently, the methods of the invention.

Furthermore, the Examiner relies on inherency as the basis for asserting that the compounds of Gaster act by the claimed biochemical mechanism. The Examiner cites *In re Swinhart*, 169 USPQ 226 (CCPA 1971) as standing for the proposition that "a newly discovered property does not necessarily mean that the product is unobvious, since the property may be

inherent in the art." Applicants agree that a newly discovered property does not necessarily make a composition claim patentable over the art. However, the claims at issue in the present case are method claims, not composition claims, and Gaster is being cited for obviousness. In order to serve as a reference for obviousness, the prior art must provide motivation and a reasonable expectation of success. However, "obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." MPEP 2141.02, citing *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993). At the time of the invention, KCNQ channel openers were not recognized as methods of treating anxiety. The compounds of Gaster are not disclosed as having KCNQ channel openers activity.

Finally, the MPEP § 2112(IV) states that to establish inherency, the extrinsic evidence

[M]ust make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of skill in the art. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. *In re Robertson*, 49 USPQ2d 1949 (Fed. Cir. 1999).

This legal standard has not been met by the present rejection.

**Gaster Fails to Explicitly or Inherently Teach a Method of Reducing Anxiety by Opening KCNQ Potassium Channels**

The Examiner asserts that the aryl carbamoyl compounds of Gaster are used to treat anxiety and, therefore, inherently increase ion flow through KCNQ potassium channels. See page 13, line 13 of Examiner's Office Action mailed August 25, 2004. Applicants respectfully disagree with the Examiner's assertion on page 3, line 15-21 of the Office Action that the aryl carbamoyl compounds of Gaster can be used to treat anxiety, as there is no experimental evidence in Gaster that these compounds actually treat anxiety. Although the Gaster asserts that the claimed compounds can be used to treat anxiety, along with numerous

other disease states related to CNS disorders, there is no experimental data that any of the claimed compounds can be used to treat any disease, let alone anxiety.

Furthermore, there is no evidence that the compounds inherently increase ion flow through KCNQ potassium channels. Applicants respectfully note that it is likely anxiety is caused by multiple mechanisms in addition to increasing ion flow through KCNQ potassium channels. Therefore, some compounds that are used to treat anxiety, including currently marketed medications, do not act as KCNQ openers.

The MPEP states: "The fact that a certain result or characteristic *may* occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." See MPEP §2112 (emphasis in original), quoting *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). Inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." See MPEP §2112, quoting *In re Robertson* 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Furthermore, "[i]n relying upon a theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." See MPEP §2112 (emphasis in original), quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Here, Gaster provides no evidence that the disclosed aryl carbamoyl compounds actually reduce anxiety, much less through increasing ion flow through KCNQ potassium channels. Rather, Gaster merely asserts, but does not show experimentally, that "certain compounds of the invention exhibit 5HT<sub>2B</sub> antagonist activity." See column 1, lines 20-21. Applicants acknowledge Gaster's statement that 5HT<sub>2B</sub> antagonists "are believed to be of *potential* use in the treatment of CNS disorders, such as anxiety . . . ." See column 1, lines 21-23. However, Gaster never demonstrates that the disclosed aryl carbamoyl compounds are, in fact, able to treat anxiety. Moreover, no examples are provided in which any of the disclosed aryl carbamoyl compounds are shown to exhibit anxiety reducing characteristics. Therefore, one of skill in the art, after reading Gaster, would conclude that aryl carbamoyl compounds *may* be useful in the treatment of anxiety, but are not *necessarily* capable of reducing anxiety. Because

the aryl carbamoyl compounds are not *necessarily* capable of reducing anxiety, inherency cannot be sufficiently established. See MPEP §2112, quoting *Ex parte Levy* and *In re Rijckaert*.

Assuming, arguendo, that the disclosed aryl carbamoyl compounds are capable of reducing anxiety, Applicants submit that there is no basis in fact and/or technical reasoning to reasonably support the determination that the aryl carbamoyl compounds *necessarily* increase ion flow through KCNQ potassium channels. Anxiety is a complex disease, like cancer, high blood pressure, heart disease, and depression. Applicants respectfully note that as a complex disease, it is likely that anxiety can be treated by therapeutic agents acting via different biochemical mechanisms, just as cancer, high blood pressure, heart disease, and depression are treated with medicines having different mechanisms and effects. Therefore, not all methods of reducing anxiety would be expected to work by increasing ion flow through a KCNQ potassium channel.

The Examiner has provided no basis or reasoning to support the assertion that a compound that reduces anxiety by antagonizing 5HT<sub>2B</sub> receptors necessarily increases ion flow through KCNQ potassium channels. Nor is such basis or reasoning provided in Gaster or in Applicants' disclosure. Therefore, Applicants request that the Examiner provide a basis and/or reasoning to conclude that the aryl carbamoyl compounds *necessarily* increase ion flow through KCNQ potassium channels or withdraw the rejection.

5HT<sub>2C</sub> receptor antagonism is the only reported activity for these aryl carbamoyl compounds. One skilled in the art would immediately recognize that 5HT<sub>2c</sub> receptors radically differ in structure and function from KCNQ potassium channels. Therefore, there is no reason for one of skilled in the art to conclude, *a priori*, that the 5HT<sub>2C</sub> receptor antagonists disclosed by Gaster would function to open KCNQ channels. To find otherwise requires the exercise of impermissible hindsight reconstruction of the prior art. See *W.L. Gore & Associates Inc. v. Garlock Inc.*, 220 USPQ 303, 313 (Fed. Cir. 1983) (stating, "[t]o imbue one of ordinary skill in the art with knowledge of the invention in suit...is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher"). The only motivation to look to the compounds of Gaster is found in the Applicants specification.

5HT<sub>2C</sub> receptors belong to the class A or rhodopsin-like G-protein-coupled receptors (GPCRs), a seven-transmembrane domain protein family. In response to chemical or physical external stimuli, GPCRs undergo a conformational change directly leading to the activation of heterotrimeric G-proteins and other intracellular signaling mediators. By contrast, KCNQ channels do *not* belong to the GPCR family. Rather, KCNQ channels are composed of KCNQ subunits that are members of the Kv superfamily of potassium channel monomers. The KCNQ subunits form pores, allowing ions to pass in a voltage dependent manner, which does not directly lead to activation of heterotrimeric G-proteins. Because of the divergent structure and function of 5HT<sub>2C</sub> receptors and KCNQ channels, there is no reason to expect a 5HT<sub>2C</sub> receptor antagonist to increase ion flow through a KCNQ potassium channel.

Because one of skill in the art would have no reasonable expectation of successfully using the 5HT<sub>2C</sub> receptor antagonists of Gaster to treat anxiety by increasing ion flow through KCNQ potassium channels, Applicants respectfully request withdrawal of the rejection.

#### **Double Patenting Rejection**

The Examiner has rejected claims 45-57 under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349. Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349 in view of Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-82 also stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claim 22 of US Patent 6,495,550 and claims 30-59 of US Patent 6,737,422.

With respect to the rejection over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349, if necessary a terminal disclaimer will be filed in accordance with 37 CFR §1.321, should the claims be deemed otherwise allowable. Until such time, Applicants request that the rejection be held in abeyance.

With respect to the rejection over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349 in view of Gaster, U.S. Patent No. 6,235,758, as argued above, the present invention is not obvious over Gaster. As the combination of McNaughton-Smith and Gaster do not render the present claims obvious, Applicants request that the rejection be withdrawn.

With respect to the rejection over claim 22 of US Patent 6,495,550, if necessary a terminal disclaimer will be filed in accordance with 37 CFR §1.321, should the claims be deemed otherwise allowable. Until such time, Applicants request that the rejection be held in abeyance.

With respect to the rejection over claims 30-59 of US Patent 6,737,422, the Examiner asserts that it would have been obvious to the skilled artisan that the disorder of anxiety would fall under the breadth of psychotic disorders. Applicants respectfully traverse. According to DSM III, American Psychiatric Association: Diagnostic and Statistic Manual of Mental Disorders, Third Edition, Revised, Washington, DC, American Psychiatric Association, 1987, anxiety disorders and psychotic disorders are different classes of disease, and so anxiety does not fall under the "breadth" of psychotic disorders. The current DSM IV does not change this classification. For example, psychotic disorders can be classified as: Organic Mental Disorders (290.00, 290.20, 290.21, 290.30, 290.10, 290.11, 290.12, 290.13, 290.4x, 291.40, 291.80, 291.00, 291.30, 291.10, 291.20, 303.00, 305.70, etc.); Schizophrenia (295.1x, 2x, 3x, 9x, and 6x for different types); Delusional Disorders (297.10); Mood Disorders with Psychotic Features (296.4x, 5x, 6x, 301.13, and 300.40), and Psychotic Disorders not Elsewhere Classified, further divided into Brief Reactive Psychosis (298.80), Schizophreniform Disorder (295.40), Schizoaffective Disorder (295.70), and Induced Psychotic Disorder (297.30). In contrast, Anxiety Disorders can be classified as: Panic Phobia with Agoraphobia (300.21); Panic Phobia without Agoraphobia (300.01); Agoraphobia without History of Panic Disorder (300.22); Social Phobia (300.23); Simple Phobia (300.29); Obsessive Compulsive Disorder (300.30); Post-Traumatic Stress Disorder (309.89); and Generalized Anxiety Disorder (300.02). Applicants therefore respectfully request that the rejection be with drawn.

Appl. No. 09/939,230  
Amdt. dated 2/24/05  
Reply to Office Action of August 25, 2004

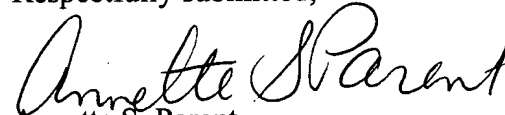
PATENT

**CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

  
Annette S. Parent  
Reg. No. 42,058

TOWNSEND and TOWNSEND and CREW LLP  
Two Embarcadero Center, Eighth Floor  
San Francisco, California 94111-3834  
Tel: 415-576-0200  
Fax: 415-576-0300  
60426340 v1